DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

WARNING LETTER

VIA FEDERAL EXPRESS

NOV 22 2004

Majid Moshirfar, M.D.
University of Utah
Moran Vision Center
6360 South 3000 East
Suite E
Salt Lake City, Utah 84121

Dear Dr. Moshirfar:

The purpose of this Warning Letter is to inform you of objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at your clinical site. This letter also discusses your written response, dated June 30, 2004, to the noted violations and requests that you implement prompt corrective actions. Mr. Thaddeus M. Steinke, an investigator from FDA's Denver District Office, conducted the inspection from June 6 through June 18, 2004. The purpose of the inspection was to determine if your activities as a clinical investigator for the [redacted] study complied with applicable FDA regulations. The [redacted] is a device defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 321(h)].

The FDA conducted the inspection under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval (PMA) applications, and Premarket Notification [510(k)] submissions are scientifically valid and accurate. The program also ensures that human subjects are protected from undue hazard or risk during scientific investigations.

Our review of the inspection report prepared by the district office revealed serious violations of Title 21, Code of Federal Regulations (21 CFR), Part 812 – Investigational Device Exemptions, 21 CFR Part 50 – Protection of Human Subjects, and Section 520(g) of the Act. At the close of the inspection, Mr. Steinke presented a Form FDA 483 "Inspectional Observations" to you for review and discussed the listed deviations. Ms. Deborah Harrison, Director of Clinical Studies was also present, and Ms. Georgie Lewis, Site Manager was present for a portion of the discussion. The deviations noted on the FDA 483, your written response, and our subsequent inspection report review are discussed below:

Failure to report adverse events in a timely manner and to conduct the investigation in accordance with the investigational plan (21 CFR 812.100 and 812.110(b)).

Clinical investigators are required to ensure that investigations are conducted according to the signed agreement, the Investigational Plan, and applicable FDA regulations, as

well as any conditions of approval imposed by the IRB or FDA pursuant to 21 CFR 812.110(b). The study protocol is part of the Investigational Plan (21 CFR 812.25(b)).

In several instances, you failed to report adverse events as required by the protocol. Examples of this failure include but are not limited to the following:

- An Adverse Event (AE) was not reported to the sponsor or to the IRB in a timely manner. For example, following implantation on [redacted], patient [redacted] had a [redacted] that was not reported to the IRB until [redacted] No case report forms were sent to the sponsor until [redacted] Following [redacted] was not returned to the sponsor for evaluation until [redacted] An Adverse Reaction Report was only signed by you and dated [redacted] and an Adverse Event (AE) Report was only signed and dated by you on [redacted]. The IRB did not receive these reports until [redacted] Patient [redacted] subsequently developed a [redacted]) following [redacted] which was not reported to the IRB as an Adverse Event. [redacted] took place on [redacted] In your response, you state that the late adverse event report for patient [redacted] was discovered during a routine internal chart audit in [redacted], and that corrective action was taken at that time to file the correct reports and to ensure that adverse event reporting guidelines were followed, and at that time no further action was deemed necessary. You further state that an [redacted] following [redacted] surgery, possibly secondary to [redacted], is an expected potential complication and is stated as such in the informed consent. The sponsor, however, considered the [redacted] to be an adverse event, and expressed concerns that the [redacted] was related to not fully removing [redacted] The sponsor's monitoring records indicate that the operative and post-operative reports were requested by them on [redacted] Post-operative Complication/Adverse Event Guide lists [redacted] as a complication.

- A [redacted] for patient [redacted] was apparently not reported to the sponsor in a timely manner as an adverse event.

- Patient [redacted] had an [redacted] An Adverse Reaction Report for this patient with a date of [redacted] was sent to the sponsor; however, the date is in question because the Facsimile date on the form is [redacted], which gives the appearance that the form was FAXed before the date of the Adverse Reaction Report. Please clarify the dates the adverse events were reported. The form describes a number of adverse events for patient [redacted] including [redacted] The [redacted] was not

[redacted] during a secondary surgery on [redacted]. You sent an AE report to the IRB dated [redacted] and it was stamped as being received by the IRB on [redacted]

Your response states that the corrective action regarding the adverse event was taken during the routine internal audit in [redacted] and that this event was also considered a surgical complication rather than a reportable adverse event. Though the secondary surgical intervention was reported as an adverse event, the report was not sent to the sponsor until [redacted] You agreed during the closeout discussion that adverse events should be reported to both the sponsor and IRB in a more timely manner. Please provide us with an explanation as to the specific steps or preventive practices which you are taking or have taken to prevent the recurrence of late reporting in ongoing and future studies.

Patients did not always have their [redacted] determined at the intervals specified by the protocol. Examples include but are not limited to the following:

- In patient [redacted] patient file, the only [redacted] documented occurred on [redacted] This patient had a [redacted] and underwent secondary surgery for [redacted] The protocol requires that [redacted] be done at visits 4, 6, and 7, which correlates to post-operative visits at 4-6 months, 12-17 months, and 18-24 months. You state in your response that patient [redacted] was exited from the study when the study [redacted] was [redacted] -- or prior to the 6 month post-operative visit, the time specified for [redacted] determination -- and no further action was indicated. We note that post-operative reports were completed for the patient on [redacted], and no [redacted] were done at any of these visits.

- Your study site did not record the [redacted] or the other additional procedures at the 4 month visit for patient [redacted] during the four month post-operative visit of [redacted] Futhermore, there was a lab report, but it was not recorded on the appropriate form, nor did your study site record [redacted] as is required at visits 4 and 6. Although the timeframe for visit six has passed, there were no further [redacted] for this patient's [redacted]

Your response states that you have updated the case report form with all the information that was collected during visit 4 for patient [redacted] and provided it to the sponsor. Please provide FDA with a copy of the corrected case report form, and the steps that you plan to take or have taken to prevent further violations of recordkeeping requirements. You also state that visit 6 (12-14 months post-operative) was the most current visit for this patient.

It took place on [redacted] the time during which your [redacted] was out of operation and [redacted] were not obtained. You indicate that [redacted] will be performed at the next scheduled visit at 22-26 months. See our further comment below regarding the [redacted]

During the inspection, there appeared to be disagreement about whether the [redacted] that was used for the [redacted] was broken down for approximately one month or several months. You stated: 1) the [redacted] was out of operation for a period of time during [redacted] and [redacted] were not obtained; 2) the vendor was unable to provide a loaner, and no other [redacted] practice in Utah owns this type of equipment; and 3) the [redacted] is now operational, and you have obtained and are continuing to obtain [redacted] as patients attend their next scheduled visit. As this is an essential piece of equipment for this type of study, preventative steps should be taken to prevent a similar situation.

All data needed to assess the status of a patient was not recorded, as required by the sponsor and protocol. Examples include the following:

- The Patient Qualification [redacted] Form for patient [redacted] was missing information that should have been collected during the pre-operative visit for her [redacted]. No values were entered for [redacted] Surgery was performed on [redacted] The same values were missing for the post-operative visit on [redacted] You state that the clinic staff has been instructed that proper research conventions require that either '0' or 'none' be indicated rather than omitting values, and case report forms will be completed accordingly from now on. We find this response acceptable.

- In our review of the Establishment Inspection Report, the FDA investigator also noted that the 1-6 day visit record was dated [redacted] although the visit occurred on [redacted] In addition, the Patient Qualification [redacted] Form dated [redacted] which is intended to be completed before surgery, was missing data for the [redacted] The questions regarding the [redacted] and the [redacted] were not answered. The sponsor faxed back the form with arrow pointing to the missing data. Although the surgery was scheduled for [redacted] the CRF was not corrected until [redacted] The Preoperative/Operative page of the CRF did not answer the question [redacted] The sponsor faxed this form back for data correction on [redacted]

The protocol was not always followed for post-operative visits, as follows:

- Patient [redacted] did not make her scheduled visit on [redacted] and as of June 8, 2004, there have been no other visits. There was no documentation of attempts

to contact the patient since then. You state in your response that attempts were made to contact this patient by phone, and the patient had not responded. You confirm that a record of the contact attempts was not included in the patient's chart, that you are continuing to attempt to contact the patient, and documentation of this will be filed in the chart. Please advise us as to whether this patient has been contacted and/or the current status.

- Patient [redacted] had her [redacted] She did not make her visit 2 at 2-3 weeks, her visit 3 at 4-8 weeks, or a visit scheduled for [redacted] which would have been 13 months for the [redacted] and 3 months for the [redacted] Criteria for Exclusion #3 was "Patients that are not able to meet the extensive post-operative evaluation requirements." Your study site then re-enrolled the patient and [redacted] and again she has not made clinic visits. Although an [redacted] in Portland, Oregon, did examine her for her [redacted], all information necessary for the CRF was not collected and reported.

You state in your response that, prior to enrolling the patient, the importance of post-operative follow-up was stressed and it was your understanding that the patient intended to meet these requirements despite living out of town. After [redacted], the patient determined she could no longer meet the visit schedule. At that time, you chose to continue the patient's participation and collect as much data as possible for the study. The patient agreed to see anothe[redacted] in her local area, and you did obtain clinical information from those visits. However, all information necessary for the CRF was not collected and reported by the other [redacted] This patient should have been excluded; instead she was enrolled again and her [redacted] Please provide us with an explanation as to the specific steps or preventive practices which you are taking or have taken to prevent the recurrence of this deviation in ongoing and future studies.

Recent patient preoperative history was not obtained per the protocol, as follows:

Patient [redacted] was initially evaluated on [redacted]. A Preoperative/Operative form for [redacted] showed a presurgical examination date for this patient of [redacted], and an operative report date of [redacted] The [redacted] recorded are the same for the initial evaluation and for the [redacted] pre-operative exam. However, FDA investigators found no source data for the pre-operative exam and thus no documentation that a pre-operative examination occurred. The patient's [redacted] with the [redacted] On the Patient Qualification & [redacted] Form, you indicated that you used the data from the pre-operative exam on [redacted] This statement, the lack of source data, and the unchanged [redacted] contradict your statement in your response that a new pre-operative exam occurred on [redacted]

Failure to use the specified informed consent form when patients with exclusion criteria were enrolled and failure to have the proper currently approved version of the informed consent form signed prior to entry into the study and performing surgical implants of the test article (21 CFR 812.100, 812.140(a)(3)(i) and 21 CFR 50.20 and 50.27).

Informed consent must be obtained from the subject or the subject's legally authorized representative prior to his or her participation in an investigational study, in accordance with 21 CFR Part 50. This includes obtaining the subject's or the legally authorized representative's signature indicating that the study subject has been informed of the risks and benefits of participating in the clinical trial. The informed consent must be signed and dated by the subject or the subject's legally authorized representative at the time of consent, and a copy given to the person signing the form (21 CFR 50.27). In addition, pursuant to 21 CFR 812.140(a)(3)(i), investigators are responsible for maintaining accurate records evidencing informed consent.

The inspection found several instances in which you did not adhere to informed consent requirements. A review of patient records revealed the following:

- On October 9, 2002, your study site received the Protocol Deviation Substudy Addendum to the [redacted] Clinical Study from the sponsor. This states: "Important: Subjects must sign this Addendum and the Standard [redacted] Informed Consent to be included in the [redacted] Protocol Deviation Study." Patients who had exclusion criteria, such as [redacted] greater than the protocol-specified [redacted] were accepted into the study and were [redacted] but did not sign the Patient Informed Consent Addendum.

  Acceptance of these patients seems to contradict information presented to the IRB for IRB continuing review approval that indicated that subjects would be excluded due to 28 exclusion criteria, including the criteria identified above. In your response, you note that the protocol statement of the exclusion criteria permits the surgeon to exercise discretion in evaluating the clinical significance of deviation from the criteria. Also, you state that, following your internal audit in July 2001, you instituted a process for the site study coordinator to verify, prior to ordering a study [redacted] and scheduling surgery, that the appropriate informed consent has been obtained from patients. Please provide us with a copy of the procedures you have instituted for the study coordinator to ensure that appropriate informed consent has been obtained from the patients.

- Consent forms for two patients who received [redacted] pursuant to compassionate use IDEs did not contain required information. Specifically, in a

letter dated June 20, 2002, FDA approved a protocol deviation for these procedures, provided the informed consent met certain conditions:

> The consent form used should provide information addressing the following issues: the patients' high-risk [redacted] limited long-term information regarding the [redacted] effect on the [redacted], and possible [redacted] in the future necessitating another [redacted] (If appropriate, the study consent form may be used with an addendum to inform the patient of concerns specific to their situation.)

The patient files for [redacted] patients [redacted] and [redacted] contained a consent form that was not modified per these instructions. Further, on [redacted] patient [redacted] signed a version of the consent that had expired on August 21, 2002. We also note that both of these patients developed [redacted] following [redacted] and that for both patients the condition persists.

You stated in your response that you followed the general guidelines for a protocol deviation provided by the sponsor in a memorandum dated April 14, 2000, but inadvertently missed the correspondence from FDA concerning specific modification of the informed consent. You state this oversight might have been due to a failure to communicate all correspondence between the principal investigator's remote office location and the regulatory coordinator's office at the Moran Eye Center. You state that, in the future, the regulatory coordinator will work directly with the study sponsor to assure that all requirements are met. Please provide us with written details and/or procedures as to how this correction will be accomplished.

- Patient [redacted] signed the informed consent form on [redacted] seven days after his surgery on [redacted]
- Informed consent forms were completed retroactively for patients [redacted]
- Several patients signed versions of the consent form that expired before the [redacted] surgery. For example, on [redacted] patient [redacted] signed a version of the consent form that had expired on August 12, 2000. Other patients that signed incorrect versions of the consent forms include the following: [redacted]

In your response to these observations, you state that all subjects received and signed an informed consent prior to surgery and that patients with missing forms were asked to re-sign them. The response describes corrective measures including immediately securing the signed consent form to the inside front cover of the patient chart to avoid misplacement. You also state that you have addressed the issue of ensuring that the most

recently approved version of the informed consent is signed by having the site study coordinator verify documentation prior to ordering a study [redacted] and scheduling surgery. We suggest a checklist to facilitate document verification. Otherwise, your response is adequate.

Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation (21 CFR 812.140).

FDA regulations require investigators to maintain accurate, complete, and current records relating to the investigator's participation in an investigation (21 CFR 812.140(a)). *Numerous examples of study data omissions, inaccuracies and inconsistencies were observed in your study records, including, but not limited to, the following:*

- Patient [redacted] post-operative exam of [redacted] found a [redacted] the severity ranking of which was changed from [redacted] to [redacted] The change was scribbled out, and not dated, nor were these changes initialed by the responsible party.

- Patient [redacted] Patient Qualification & [redacted] Form dated [redacted] contained crossouts and scribbles which obliterated the underlying data. The changes were not dated or initialed.

- For patient [redacted] there were several crossouts and over-writes on the Preoperative/Operative form. The value for [redacted] has been scribbled out and is not readable. It was replaced by [redacted] an acceptable value.

- Inaccurate information was noted for patient [redacted] This patient reportedly did not have a previous [redacted] emoved. However, a consent form for the University of Utah John A. Moran Eye Center refers to [redacted] The Operative Report dated [redacted] lists the Operation Performed as [redacted] ..." The Preoperative Assessment Report dated [redacted] listed the reason for procedure as [redacted] and the procedure as [redacted]

- Inaccurate information for patient [redacted] was noted. This patient reportedly did not have a previous [redacted]. However, a consent form for the University of Utah John A. Moran Eye Center refers to [redacted] The Operative Report for the [redacted] procedure listed the Operation Performed as [redacted] The Op Report for the [redacted] procedure mentions [redacted] The PreOp Assessment Report dated [redacted] lists the reason for procedure as [redacted] and the Procedure as [redacted] Also in the patient's file was a [redacted]

[redacted] Revised March 13, 2002, "Utilized for all [redacted] surgical patients who have a[redacted]

- For patient [redacted], the implant surgery operative report was dated [redacted], but the date of surgery that appeared on the [redacted] Preoperative/Operative CRF was [redacted] the same date the form was signed. In addition, the [redacted] Form for visit 6 occurred on [redacted] but on an evaluation the study coordinator recorded the date as [redacted]

- The Patient Medical History Questionnaire (which is reportedly taken at the initial visit) was not signed by the physician or dated for several patients, including patients [redacted]

You state in your response that staff and physicians neglected to follow Good Clinical Practice guidelines to cross through, initial, and date changes. You indicate that over the past year, the University of Utah School of Medicine has taken steps to provide training, has instituted a Research Compliance Officer position, and established a Task Force. **FDA may verify the adequacy of these corrections during a future inspection.**

There appears to have been an overall problem with careless recordkeeping, including late entries, misdated, undated, and unsigned documents. As a Clinical Investigator, you must ensure that any staff or personnel who are delegated study tasks are adequately supervised by you to ensure conformance with the investigational plan. You must also ensure that all study data and records are correctly collected and maintained. We caution you that recordkeeping problems could make the validity of data questionable.

In addition to the FDA 483 Observations, the FDA investigator also discussed with you that patients meeting Protocol Criteria Exclusions #6 and #14 were [redacted] with the [redacted] The exclusions pertained to patients with a [redacted] or family history of [redacted] and patients with [redacted] or a family history of [redacted], respectively. There were no protocol waivers requested.

The above-described deviations are not intended to be an all-inclusive list of deficiencies that may exist in this clinical study. It is your responsibility as a clinical investigator to assure adherence to each requirement of the Act and all applicable federal regulations.

Within 15 working days after receiving this letter, please provide written documentation of the additional, specific steps you have taken or will take to correct these violations and prevent the recurrence of similar violations in current and future studies. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. Send your

response to: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch HFZ-312, 2094 Gaither Road, Rockville, Maryland 20850, Attention: Viola Sellman.

We are also sending a copy of this letter to FDA's Denver District Office, and request that you also send a copy of your response to that office. If you have any questions, please contact Ms. Sellman by phone at 240-276-0125, or by email at vxs@cdrh.fda.gov.

Sincerely yours,

Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health

Cc: [redacted] (purged copy)